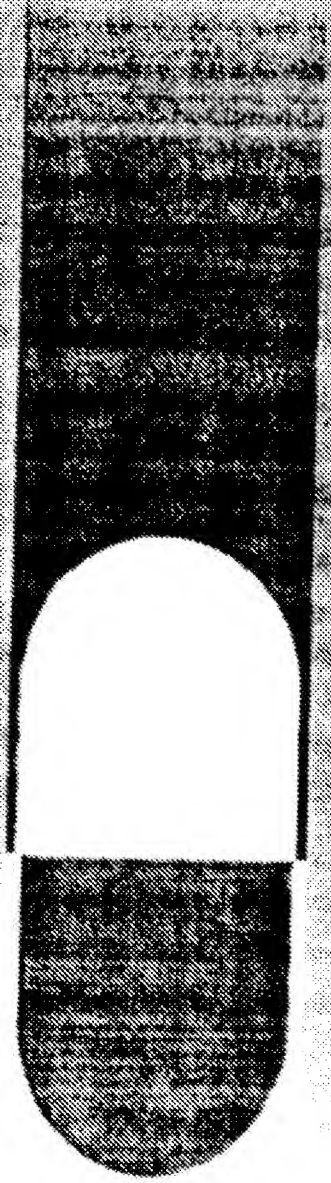
Exhibit C

Pharmaceutical Dosage Forms and Drug Delivery Systems



Howard C. Ansel
Nicholas G. Popovich
Loyd V. Allen, Jr.

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Developmental Editor: Frances M. Klass
Production Coordinator: Peter J. Carley
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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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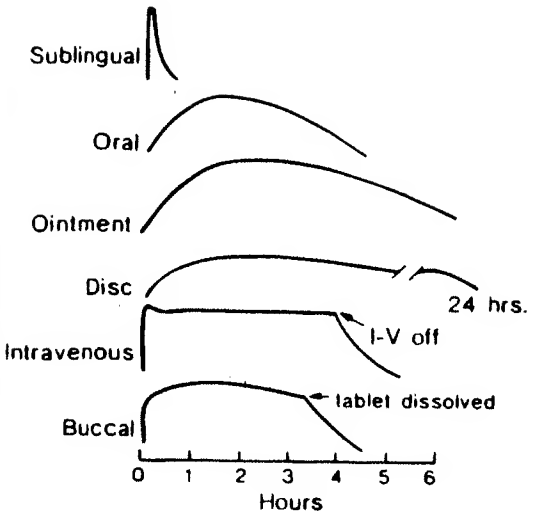

Fig. 3–11. *Blood-level curves of nitroglycerin following administration of dosage forms by various routes. (From Abrams, J.: Nitroglycerin and Long-Acting Nitrates in Clinical Practice.* The American Journal of Medicine, *Proceedings of a Symposium: First North American Conference on Nitroglycerin Therapy, June 27, 1983. Reprinted with Permission.)*

An individual drug substance may be formulated into multiple dosage forms which result in different drug absorption rates and times of onset, peak, and duration of action. This is demonstrated by Figure 3–11 and Table 3–7, for the drug nitroglycerin in various dosage forms. The sublingual, intravenous, and buccal forms present extremely rapid onsets of action whereas the oral (swallowed), topical ointment and topical disc present slower onsets of action but greater durations of action. The disc provides the longest duration of action, up to 24 hours following application of a single patch to the skin. The transdermal nitroglycerin disc allows a single daily dose, whereas the other forms require multiple dosing to maintain drug levels within the therapeutic window.

The difference in drug absorption between dosage forms is a function of the formulation and the route of administration. For example, a problem associated with the oral administration of a drug is that once absorbed through the lumen of the gastrointestinal tract into the portal vein, the drug may pass directly to the liver and undergo the *first-pass effect*. In essence a portion or all of the drug may be metabolized by the liver. Consequently, as the drug is extracted by the liver, its bioavailability to the body is decreased. Thus, the bioavailable fraction is determined by the fraction of drug that is absorbed from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver. The bioavailable fraction (f) is the product of these two fractions as follows:

f = Fraction of drug absorbed

× Fraction escaping first-pass metabolism

The bioavailability is lowest, then, for those drugs that undergo a significant first-pass effect. For these drugs, a hepatic extraction ratio, or the fraction of drug metabolized, E, is calculated. The fraction of drug that enters the system circulation and is ultimately available to exert its effect then is equal to the quantity (1 − E). Table 3–8 lists some drugs according to their pharmacologic class that undergo a significant first-pass effect when administered by the oral route.

To compensate for this marked effect, the drug manufacturer may consider other routes of drug administration, e.g., intravenous, intramuscular, sublingual, that avoid the first-pass effect. With these routes there will be a corresponding decrease in the dosage required when compared to oral administration.

Table 3–7. Dosage and Kinetics of Nitroglycerin in Various Dosage Forms[1]

Nitroglycerin, Dosage Form	*Usual Recommended Dosage (mg)*	*Onset of Action (Minutes)*	*Peak Action (Minutes)*	*Duration (Minutes/hours)*
Sublingual	0.3–0.8	2–5	4–8	10–30 minutes
Buccal	1–3	2–5	4–10	30–300 minutes[4]
Oral	6.5–19.5	20–45	45–120	2–6 hours[Ω]
Ointment (2%)	½–2 inches	15–60	30–120	3–8 hours
Discs	5–10	30–60	60–180	Up to 24 hours

[4] Effect persists so long as tablet is intact.
[Ω] Some short-term dosing studies have demonstrated effects to 8 hours.
[1] From Abrams, J.: Nitroglycerin and Long-Acting Nitrates in Clinical Practice. *The American Journal of Medicine*, Proceedings of a Symposium: First North American Conference of Nitroglycerin Therapy, June 27, 1983, p. 88.